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Safety of Early Hospital Discharge of Selected Febrile Children and Adolescents With Cancer With Prolonged Neutropenia

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Problem. The safety of early hospital discharge (i.e., before the absolute neutrophil count [ANC] exceeds 500 cell/mm^3) of febrile neutropenic children and adolescents with cancer who had experienced prolonged neutropenia (i.e., for more than 7 days) following admission has not been studied.

Method of Study. Three hundred and thirty-nine consecutive admissions of children and adolescents with cancer for management of febrile neutropenia were reviewed. Early discharge criteria included absence of fever for 24 hours prior to discharge, sterile blood cultures for 24 hours, evidence of bone marrow recovery defined as a sustained increase in platelet count and ANC or absolute phagocyte count (APC), and control of local infection if present. Children hospitalized with febrile neutropenia who remained neutropenic for more than 7 days were analyzed to assess their outcomes following discharge if they had met criteria for early hospital discharge.

Results. Thirty-three patients inwhom neutropenia had persisted for more than 7 days were discharged before attaining an ANC greater than 500/mm^3 when they met the early discharge criteria. Only two children (6%) required readmission for recurrent fever, a rate which was not different from that of patients discharged after a more transient episode of neutropenia (2 of 33 vs. 3 of 121, $P = 0.3$). Both patients who were readmitted had a source of local infection which worsened despite oral antibiotics. Both patients appeared clinically well at the time of readmission and had sterile cultures during their second hospitalization with resolution of local infection.

Conclusion. This study confirms that low-risk criteria used to select children with cancer for discharge before complete resolution of neutropenia can be safely applied to those patients whose neutropenia lasted more than 7 days following admission. **Med. Pediatr. Oncol. 28: 191–195**

Key words: fever; neutropenia; bacteremia; pediatrics; neoplasia

INTRODUCTION

Fever associated with neutropenia commonly follows cytotoxic chemotherapy administered to children with cancer or accompanies hematologic malignancies at diagnosis or relapse. Although the severity and duration of neutropenia are the most important factors contributing to this risk, the presence of a central line, mucositis, or underlying malignancy at induction or relapse can substantially affect the likelihood of fever resulting from serious infection. Hospitalization for evaluation and broad-spectrum antibiotic therapy until the patient is afebrile and no longer neutropenic (i.e., absolute neutrophil count [ANC] greater than 500 cells/mm^3) or for a minimum of 5–7 days has until recently been the standard of care [1–12]. During the past 5 years several studies have shown that some neutropenic patients are at relatively lower risk of serious infection and can be discharged before the resolution of their neutropenia [13–18]. Factors that define low-risk status include degree of bone marrow recovery [13,14], duration of fever [13–15], type of malignancy, and whether the underlying disease is in remission or relapse [13,14,16].

Patients with prolonged neutropenia, i.e., lasting for more than 7 days, are viewed as being at particularly high risk of developing bacterial and fungal infections [19–22] and might therefore not be appropriate candidates for hospital discharge prior to complete resolution of neutropenia. Most investigators recommend continuing broad-spectrum antimicrobial therapy and initiating antifungal therapy with amphotericin B until complete resolution of fever and neutropenia or for a minimum of 7–10 days [6–9,23]. We hypothesized that these patients could also be discharged before recovery of the ANC to greater than 500/mm^3 if they demonstrated the same low-risk features previously applied to patients with more transient neutropenia. Therefore, we evaluated the safety of early hospital discharge of hospitalized patients whose neutropenia had persisted for more than 7 days following admission. Our results indicate that these patients may be safely

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discharged after a febrile event prior to full recovery from neutropenia utilizing the same criteria employed for patients with more transient episodes of neutropenia.

MATERIALS AND METHODS

Patient Population

All children and adolescents admitted to Children's Medical Center of Dallas with febrile neutropenia were eligible for discharge before complete resolution of their neutropenia if they met certain low-risk criteria which are defined below. These children were being treated according to a variety of Pediatric Oncology Group (POG) and local institutional chemotherapeutic protocols. Patients who had undergone bone marrow transplantation (BMT) were excluded. Fever was defined as a single oral or axillary temperature of greater than 38.5°C or two measurements of greater than 38.0°C in a 24-hour period [1]. Neutropenia was defined as an ANC of less than 500 cells/mm^3 (ANC = 0.01 × [% bands + % polymorphonuclear cells] × total white blood cell [WBC] count).

Diagnostic Evaluation

The initial evaluation of all patients included a history and physical examination. Laboratory evaluation at study entry included an electronically measured complete blood count (CBC) with a manual differential WBC count, determination of the ANC and absolute phagocyte count (APC = 0.01 × [% bands + % polymorphonuclear cells + % monocytes] × total WBC), blood cultures from each lumen of any central venous catheter and/or from a peripheral vein, and other cultures or diagnostic tests as clinically indicated.

All patients were admitted to the hospital. Intravenous antibiotic therapy with a third-generation cephalosporin was administered immediately after blood cultures were obtained. Vancomycin was not routinely used in the initial empiric regimen. Additional antibiotics were administered for specific indications (e.g., mucositis, typhlitis, etc.). Daily CBCs were obtained, and ANC and APC were calculated. Blood cultures were repeated daily if the child's temperature was greater than 38.5°C. Changes in the antibiotic regimen or addition of empiric antifungal therapy were made based on clinical assessment and/or culture results and the antimicrobial sensitivity of the organism(s) isolated.

As per our standard institutional management plan, patients were eligible for discontinuation of antibiotics and discharge prior to attaining an ANC greater than 500 cells/mm^3 if they exhibited all of the following low-risk characteristics: well appearance, afebrile for at least 24 hours, sterile blood cultures, control of local infection (defined as improvement in local signs of inflammation, e.g., erythema, induration, and tenderness), and evidence of bone marrow recovery, defined as any sustained increase in platelet count and in ANC or APC. Children who were treated for bacteremia could be discharged before resolution of neutropenia after a course of intravenous antibiotics if repeat blood cultures were sterile and they otherwise met the low-risk criteria. Children were discharged on oral antibiotics for continued treatment of a localized infection. Prophylaxis against *Pneumocystis carinii* pneumonia (PCP) was resumed after discharge. Patients were considered to have recurrent fever if a febrile episode occurred within 7 days from the time of discharge. Patients who developed recurrent fever after discharge were carefully reevaluated and if they remained neutropenic were readmitted for close observation and intravenous antibiotics.

Statistical Analysis

Fisher's exact test and Chi square test were used to determine statistical differences between proportions of patients. A P value of less than 0.05 was required to reject the null hypothesis. Standard error was calculated when appropriate.

RESULTS

Patient Characteristics

Three hundred and thirty-nine consecutive episodes of febrile neutropenia occurring in 179 patients between July 11, 1991 and February 4, 1994 were reviewed and their characteristics are summarized in Table I. Of the 339 admissions, 258 children were receiving trimethoprim-sulfamethoxazole (TMP-SMZ) 3 days a week and 81 (24%) children were receiving monthly aerosolized pentamidine for PCP prophylaxis as part of a prospective study examining its safety and efficacy [24]. Of the 339 admissions, 151 children were discharged after complete resolution of neutropenia and 188 before complete resolution of neutropenia. Episodes in both groups of patients were similar in terms of age and gender. Patients who were discharged with an ANC less than 500/mm^3 were more likely to have had a hematologic malignancy, a central venous access device, and no prior therapy with a hematopoietic growth factor. In 41 (28%) instances the child was discharged on oral antibiotics, and 4 (2%) were discharged on intravenous antibiotics to complete therapy for documented bacteremia.

In 33 episodes children were discharged with an ANC less than 500/mm^3 despite prolonged neutropenia for more than 7 days after an initial febrile event (Table II). Eighty-eight percent of these episodes occurred in children with hematologic malignancies. The average number of days of fever was 5 ± 1.8 days and the average number of days of documented neutropenia was 9.8 ± 0.8 days.

Children Discharged Before Resolution of Neutropenia

In 151 of 339 (45%) episodes, children were discharged after attaining an ANC greater than 500/mm^3,

TABLE I. Characteristics of 339 Episodes of Fever and Neutropenia in 261 Children With Cancer

	Discharge ANC				
	≥500/mm³ (%)		<500/mm³ (%)		*P* value
No. of episodes	151		188		
No. of patients	98		143		
Mean age (years)	7.9		7.9		
No. of episodes with fever and neutropenia >7 days	34		40		0.97
Sex					
Male	86	(57)	116	(62)	0.72
Female	65	(43)	72	(38)	
Underlying malignancy					
Hematologic	81	(53)	135	(72)	0.003
Solid tumors	70	(47)	53	(28)	
Prior G-CSF therapy	64	(42)	28	(15)	0.00001
Empiric amphotericin B	16	(46)	8	(20)	0.03
Venous access device					
Subcutaneous	108	(72)	120	(64)	0.67
External	22	(14)	22	(12)	0.83
None	21	(14)	46	(24)	0.05
Infectious disease diagnosis					
Fever, no source	80	(53)	133	(71)	0.002
Sepsis/bacteremia	39	(26)	14	(8)	0.97
Focal infection[a]	30	(20)	38	(20)	0.83
Other[b]	2	(1)	3	(1)	
Readmission rate	8	(5)	11	(6)	0.99

[a]Focal infections include otitis media, upper respiratory tract infection, pneumonia, cellulitis, mucositis, etc.
[b]Other: one episode of cytomegalovirus infection, four episodes of herpes zoster.

TABLE II. Characteristics of 33 Children Discharged Before Attaining an ANC ≥500/mm³ After Presenting With Fever and Remaining Neutropenic for More Than 7 Days

Mean age (years)	10 (range 2.5–17)
Diagnosis	
Hematologic	29 (88%)
Solid tumors	4 (12%)
Receiving	
Hematopoetic growth factors	6 (18%)
Amphotericin B	7 (21%)
Venous access device	
Present	29 (88%)
Absent	4 (12%)
No. of days in hospital	11 ± 2.6[a]
Duration of fever (days)	5 ± 1.8[a]
Duration of neutropenia (days)	9.8 ± 0.8[a]
Discharge ANC (/mm³)	156 ± 11[a]
Discharge APC (/mm³)	416 ± 19[a]
Discharge platelet count (/mm³)	92 ± 10[a]
Infectious disease diagnosis	
FUO	17 (52)
Sepsis/bacteremia	8 (24)
Focal infection	7 (21)
Other[b]	1 (3)

[a]Mean ± standard error.
[b]Patient with prolonged aplasia and documented cytomegalovirus infection.

and 8 (5%) required readmission for recurrent fever. One hundred and twenty-three children met the early discharge criteria and were discharged with an ANC less than 500/mm³, three of whom (2%) required readmission with recurrent fever. There was no difference in the readmission rate between the two groups of patients (8 of 151 vs. 3 of 123, $P = 0.4$). The three children readmitted with recurrent fever in the early discharge group appeared well at the time of readmission and had negative cultures. All were discharged after the second hospitalization without complications. The mean number of hospital days for the early discharge group was 4 days less than those discharged after attaining an ANC of 500/mm³ (5.4 vs. 9.4 days).

One hundred and twenty-eight patients were receiving TMP-SMZ and 60 were receiving aerosolized pentamidine for PCP prophylaxis. There was no significant difference in the readmission rate between those children with febrile neutropenia who received TMP-SMZ or pentamidine (9 of 128 vs. 2 of 60; $P = 0.5$).

Patients With Prolonged Neutropenia

During 33 episodes of febrile neutropenia, patients were hospitalized for greater than 7 days but then met criteria for early hospital discharge despite persistent neutropenia. The average length of hospitalization was

11 ± 1.2 days. Patients were febrile for an average of 5 ± 1.8 days. Seven children were discharged on oral antibiotics to complete therapy for a local infection.

Only 2 of 33 patients with prolonged neutropenia (6%) required remission for recurrent fever. One child had group A beta-hemolytic streptococcal cervical lymphadenitis that initially responded to intravenous antibiotics but worsened during oral antibiotic therapy despite a rising ANC at the time of readmission. He completed a 21-day course of intravenous antibiotics after discharge. The second child was readmitted with fever and worsening mucositis despite a rising ANC. Blood cultures from both patients were sterile during the second admission. There was no difference in the readmission rate between these episodes and those following discharge after a more transient episode of neutropenia (2 of 23 vs. 3 of 121, $P = 0.3$). Eight of the 33 patients (24%) who had neutropenia for greater than 7 days had been treated with intravenous antibiotics for documented bacteremia; none of these children required readmission. Amphotericin therapy was stopped when patients were afebrile for at least 24 hours and had evidence of bone marrow recovery.

DISCUSSION

Children with cancer who have prolonged neutropenia (i.e., for more than 7 days) during hospitalization for treatment of a febrile event are felt to be at high risk of bacterial and fungal infections. Thus, the usual criteria used to select patients for early discharge before recovery of the ANC to greater than 500/mm^3 might not be expected to apply. In our series, however, none of the 31 children with prolonged neutropenia and no source of focal infection who were discharged with a rising ANC required readmission. Pizzo et al. [25] reported that among patients with febrile neutropenia for more than 7 days there was a significant number of patients who developed recurrent fever if antibiotics were stopped before complete resolution of their neutropenia. However, our criteria can select lower-risk patients for early discharge even among this group of patients felt to be uniformly high risk. The two patients with prolonged neutropenia who were readmitted after early discharge had local infections which failed to respond to oral antibiotic therapy. Based upon these data, children with neutropenia for more than 7 days following admission may be safely discharged before complete resolution of neutropenia and are no more likely to be readmitted for recurrent fever than those who had experienced more transient episodes (less than 7 days) of neutropenia.

In our review, most patients in the early discharge group were not receiving granulocyte-colony-stimulating factor (G-CSF) at the time of hospital admission. We speculate that G-CSF hastens granulocyte recovery to an ANC greater than 500/mm^3 so that the period of early recovery is not seen. This may also explain why a greater number of patients in the early discharge group had hematologic malignancy since most solid tumor protocols include G-CSF. The increasing frequent use of hematopoietic growth factors may decrease the number of patients who are eligible for early discharge by shortening the early recovery phase.

Another observation was that even patients with documented bacteremia could be discharged after completion of intravenous antibiotic therapy if signs of bone marrow recovery are present and these patients could be considered for home intravenous antibiotic therapy. None of these high-risk patients required readmission and none developed secondary fungemia.

The many theoretical benefits to the discharge of carefully selected low-risk patients prior to the resolution of neutropenia include reduced exposure to nosocomial pathogens and improved quality of life for these children and their families by reducing the psychologic stress of hospitalization and allowing the child to resume normal activities. The practice of early discharge is also a more cost-effective way to manage patients with febrile neutropenia [17].

CONCLUSIONS

We conclude that certain low-risk patients hospitalized for fever during a period of neutropenia may be safely discharged from the hospital irrespective of their ANC or the duration of neutropenia, provided all cultures are sterile and there is evidence of bone marrow recovery. Future prospective studies will be necessary to further refine these criteria and to determine the role of oral or home intravenous antibiotics with or without hematopoietic growth factors and the possibility of avoiding hospitalization altogether in selected patients with febrile neutropenia.

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